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Draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment"
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In 2010, OPP developed a draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" which provides the foundation for evaluating multiple lines of scientific evidence in the context of the understanding of the adverse outcome pathway (or mode of action (U.S. EPA, 2010). The draft framework, which includes two key components: problem formulation and use of the Mode of Action/Adverse Outcome Pathway (MOA/AOP) frameworks, was reviewed favorably by the SAP in 2010 (FIFRA SAP, 2010).

OPP's draft framework is consistent with updates to the World Health Organization/International Programme on Chemical Safety mode of action/human relevance framework, which highlight the importance of problem formulation and the need to integrate information at different levels of biological organization[1]. Consistent with recommendations by the NRC in its 2009 report on *Science and Decisions*[2], OPP's draft framework describes the importance of using problem formulation at the beginning of a complex scientific analysis. The problem formulation stage starts with planning dialogue with risk managers to identify goals for the analysis and possible risk management strategies. This initial dialogue provides the regulatory context for the scientific analysis and helps define the scope of such an analysis. The problem formulation stage also involves consideration of the available information regarding the pesticide use/usage, toxicological effects of concern and exposure pathways and duration along with key gaps in data or scientific information.

MOA and AOP provide important concepts in this integrative analysis. Both a MOA and an AOP are based on the premise that an adverse effect caused by exposure to a compound can be described by a series of causally linked biological key events that result in an adverse human health or ecological outcome. One of the key components of the Agency's draft framework is the use the MOA framework /AOP concept as a tool for organizing and integrating information from different sources to inform the causal nature of links observed in both experimental and observational studies. Specifically, the modified Bradford Hill Criteria are used to evaluate the experimental support that establishes key events within a mode of action or an adverse outcome pathway, and explicitly considers such concepts as strength, consistency, dose response, temporal concordance and biological plausibility in a weight of evidence analysis.

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[1] Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. 2014. New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol. 2014 Jan;34(1):1-18.

[2] NRC (National Research Council). (2009). Science and decisions: Advancing risk assessment. Washington, DC: The National Academies Press. http://www.nap.edu/openbook.php?record_id=12209

One of the recommendations of the SAP was to gain experience integrating epidemiology and human incident information into risk assessment in order to further refine the approach in the draft framework. Consistent with this recommendation, OPP did not finalize the draft framework after the 2010 SAP but instead has used in draft framework in several chemical risk assessments (atrazine, chlorpyrifos and other organophosphates, glyphosate) to gain experience. Through this experience, OPP has refined the proposed approach with an improved, more transparent grading system for epidemiology studies; the revised framework will include this grading system.

In recent years, the National Academies' National Research Council (NRC) has encouraged the agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making[3]. The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies". OPP has been collaborating across the other offices in the Office of Chemical Safety and Pollution Prevention (OCSPP) to implement systematic review. The concepts associated with fit-for-purpose systematic review such as standard methods for collecting, evaluating and integrating the scientific data will also be included in the revised, final framework.

OPP is actively working on revising and finalizing the draft framework and anticipates release of the final document within the next few months.

[3] NRC 2011. "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde"; NRC 2014. "Review of EPA's Integrated Risk Information System (IRIS) Process"